REMARKS

Applicant wishes to thank Examiner Fay for the courtesy extended to Nancy Vensko, attorney of record, on September 13, 2005. The Interview Summary Form PTOL-413 summarizes the discussion held at the personal interview. The present response to the outstanding Office Action includes the substance of the Examiner Interview.

A. Disposition of Claims

Claims 1-18 are pending in this application. Claims 1, 4, and 5, have been amended to correct a spelling error and Claim 17 has been amended to include the table incorporated by reference to a table in the specification, and thus for reasons unrelated to patentability. Support for the amendment is found throughout the specification, for example, at ¶¶ 0017 and 0031 and Table 1. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

B. Compliance with 35 USC 112/2

The issue is whether the claims are in compliance with 35 USC 112/2 as being definite. The rule is that the claims must particularly point out and distinctly claim the subject matter that applicant regards as the invention. As requested by the Examiner, Claim 17 has been amended to include the table incorporated by reference to a table in the specification, thus any perceived ambiguity resolved. The conclusion is that the claims are in compliance with 35 USC 112/2 as being definite.

C. Compliance with 35 USC 103(a)

The issue is whether the claims are in compliance with 35 U.S.C. §103(a) or unpatentable as being obvious over Laties et al., (USP 5,122,522 issued 16 Jun 1992) in view of Gwon et al. (USP 6,164,282 issued 26 Dec 2000) and Sawaya (USP 5,888,493 issued 30 Mar 1999). The rule according to MPEP 2143 is that to establish a *prima facie* case of obviousness: First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; Second, there must be a reasonable expectation of success; and Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Here, none of these factors is present thus negating a *prima facie* case of obviousness.

There was no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Laties et al., Gwon et al. and Sawaya fail to teach pirenzepine in a gel form. Laties et al. describes the use of pirenzepine for the treatment of myopia prepared as solutions and in other non-gel forms (5:61 – 6: 27). Gwon et al. describes addition of methyl cellulose to ophthalmic solutions as viscosity modifiers (5:34 – 6:5) but not for use as a gelling agent for an aqueous ophthalmic gel formulation of pirenzepine. Sawaya describes aqueous ophthalmic gel formulations but is completely silent about a gelling agent for an aqueous ophthalmic gel formulation that comprises pirenzepine. The mere fact that the prior art may be modified or combined in the manner suggested by the Patent Office does not make the modification or combination obvious unless the prior art suggested the desirability of the modification or combination. Here, there is no teaching, suggestion, or incentive to support the proposed modification or combination. This is not a case in which the motivation to modify or combine the teachings in the prior art comes from the nature of a problem to be solved leading inventors to look to references relating to possible solutions to that problem. These references do not address a problem in the prior art that pirenzepine might be prepared in any other way than as solutions and in other non-gel forms, the record does not show that gels work better than solutions, and there was no problem in the prior art with the experiments of pirenzepine for the treatment of myopia prepared as solutions and in other non-gel forms. Therefore, a person of skill in the art would not be led to modify or combine these references to achieve pirenzepine in a gel form.

There was no reasonable expectation of success. Since **Stone et al., 1991, Exp Eye Res 52: 755**, (chick model), attached, first suggested use of pirenzepine as an agent to decrease myopic progression, non-primate animal research in non-primate models has demonstrated that pirenzepine reduced the development of deprivation-induced myopia and axial elongation in non-primate animals. **Leech et al., 1995 Ophthalmic Physiol Opt 15: 351**, (chick model), attached; and **Cottriall et al., 1996, Invest Ophthalmol Vis Sci 37: 1368**, (mammalian model, tree shrew), attached. Nevertheless, in the non-human primate monkey model, while a trend was noted for pirenzepine to reduce occlusion-induced excessive axial eye elongation and myopic shift, the large degree of interanimal variability and a possible contralateral effect complicated

the data interpretation. **Tigges et al., 1999, Optom Vis Sci 76: 397**, (monkey model), attached, at p. 403, col. 1, 3rd full paragraph. Thus, the prior art of Tigges et al. 1999 discouraged the art worker from attempting to substitute primate humans for non-human primate monkeys, because it appeared that the use of pirenzepine for the treatment of myopia might not extend to the primate model. Safety and tolerability trials of up to 2% pirenzepine solution in adults did not measure efficacy and continued before the workers could be discouraged by Tigges et al. 1999. **Shedden et al., 1998, Invest Ophthalmol Vis Sci 39: S279**, (pirenzepine solution safety and tolerability), attached.

The assignee proceeded against Tigges et al. 1999 to extend the use of pirenzepine for the treatment of myopia to human primates and showed that pirenzepine gel is effective and safe in slowing the progression of myopia in children. Concentrations of 0.5%, 1.0%, and 2.0% were selected based upon an acute mydriatic study in rabbits with pirenzepine gel. **Karageozian et al., 2001, Invest Ophthalmol Vis Sci 42: S59 (Abstr Nr 330), attached**[1], note line 6-8 describing pirenzepine gel, and note credits under title reporting that study was supported by Valley Forge Pharmaceuticals. Valley Forge Pharmaceuticals is the assignee, per attached **Recorded Assignment**. Trials of safety and tolerability of pirenzepine gel in children were undertaken and good tolerability and acceptable safety profile reported. **Bartlett et al., 2003, J Ocul Pharmacol Ther 19: 271**, (pirenzepine gel safety and tolerability), attached, note p. 272, 3rd full paragraph describing pirenzepine gel, and note credits under title reporting that study was supported by Valley Forge Pharmaceuticals. Based on the good tolerability and acceptable safety profile, a double-masked, multicenter, placebo-controlled trial to evaluate safety and efficacy of 2% pirenzepine gel in slowing progression of myopia in children was conducted, and safety and efficacy was reported. **Siatkowski et al., 2004, Arch Ophthalmol 122: 1667**, (pirenzepine gel safety and efficacy), attached, note p. 1668, col. 1, last full paragraph, describing pirenzepine gel, and note p. 1674, col. 1, only full paragraph, reporting that the study was supported by Valley Forge Pharmaceuticals. Finally, another double-masked, multicenter, placebo-controlled trial to evaluate safety and efficacy of 2% pirenzepine gel in slowing progression of myopia in larger numbers of children was undertaken, and safety and efficacy was confirmed. **Tan et al. 2005, Ophthalmology 112: 84**, (pirenzepine gel safety and efficacy), attached, note p. 85, col. 1, last

[1] Declaration under 37 CFR 1.131 is attached.

full paragraph describing pirenzepine gel, and note p. 84, footnote, reporting that study was supported by Valley Forge Pharmaceuticals.

In sum, while Stone et al. 1991 first suggested use of pirenzepine as an agent to decrease myopic progression, monkey studies revealed that the use of pirenzepine for the treatment of myopia might not extend to the primate model. The assignee proceeded against the prior art to substitute primate humans for non-human primate monkeys and showed that pirenzepine gel is effective and safe in slowing the progression of myopia in children. In view of the unpredictability in the prior art, the proposed modification of extending the use of pirenzepine for the treatment of myopia to human primates did not have a reasonable expectation of success.

The prior art reference (or references when combined) do not teach or suggest all the claim limitations. Attached is WO 02/096418 (with intl search report) that published PCT/US02/13823, from which this application claims priority, and the International Preliminary Examination Report (IPER). An IPER is a formulation of a nonbinding opinion on whether the claimed invention appears to be novel, to involve an inventive step (i.e., is nonobvious), and to be industrially applicable (i.e., has utility). The IPER shows that the claims of the application meet international standards for novelty, inventive step, and industrial applicability. Also note that the IPER indicates that the "prior art does not teach or fairly suggest the viscosity and sheer [sic, shear] rate as claimed herein". While the rules set forth by the PCT are not compulsory, the IPER is compelling that the claimed invention is novel, is nonobvious, and has utility, and thus meets the U.S. standards for patentability.

For these reasons, there was no suggestion or motivation to modify or combine references to achieve the claimed invention, there was no reasonable expectation of success, and the references, whether considered alone, or in combination, fail to teach or suggest all the claim limitations, a *prima facie* case of obviousness cannot stand. The conclusion is that the claims are non-obvious over the references. Thus, the claims are in compliance with 35 U.S.C. §103(a).

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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